REMARKS

Claims 1-18 are pending in the instant application. Claims 1-5 and 13-18 have been withdrawn from consideration. Claims 6-12 have been rejected. Claims 1-5, 8 and 13-18 have been canceled. Claims 6, 9, 10 and 12 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Election/Restriction Requirement Under 35 U.S.C. §121

The restriction requirement placing the claims into Groups I to IV has been deemed proper and made final. Claims 1-5 and 13-18 are withdrawn from further consideration. Accordingly, Applicant is canceling claims 1-5 and 13-18 without prejudice, reserving the right to file continuing applications for the canceled subject matter.

II. Objection of the Specification

The specification has been objected to for not making reference to the parent patent application which is now an issued patent. Accordingly, Applicant has amended the specification to add priority to U.S Patent Application Serial No. 09/100,802, filed June 19, 1998, now U.S. Patent No. 6,294,363. It is therefore respectfully requested that this objection be withdrawn.

III. Rejections Under 35 U.S.C. §112

Claims 6-12 are rejected under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards

as the invention. The Examiner suggests that the base claim 6 is unclear in reciting "the half-life of said fusion gene". The Examiner has assumed for examination purposes that Applicant means "the half-life of the polypeptide encoded by said fusion protein". Base claim 6 is also objected to for reciting "a target cells" as there is insufficient antecedent basis for this limitation as the method is intended to be used with malignant cells. Base claim 6 further stands objected to for reciting the limitations "rapidly growing cell" and "quiescent cells" in part b) as there is insufficient antecedent basis for the limitation in the claim because part a) is directed to assessing the proliferative potential of malignant cells and not to cells as such. The relative terms of "short", "rapidly" and "longer" are also objected to as they are relative terms which render claim 6 indefinite.

As claim 6 is not drawn to a method of measuring protein half-lives, Applicant assumes that the above rejections apply to claim 10. Accordingly, claim 10 has been amended to read on a method for assessing the proliferative potential of a target cell, comprising introducing into a target cell a DNA construct encoding a fusion protein, said fusion protein comprising a UbL domain operably linked to a reporter molecule; and assessing the stability of said fusion protein, wherein a decrease in the stability of said fusion protein in said target cell as compared to a normal quiescent cell is indicative of said target cell being an actively growing cell. Support for this amendment can be found in the claims as originally filed and at pages 32-33 which teach that a Rad23-HA fusion protein (*i.e.*, a UbL domain operably linked to a reporter molecule), encoded by a DNA construct that

has been introduced into a target cell (*i.e.*, a yeast cell), exhibits a decrease in stability in actively growing cells as compared to normal quiescent cells. In light of these amendments, Applicant respectfully requests that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 6-12 also stand rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner suggests that the structure and function of the claimed fusion proteins is not sufficiently described in the application. It is suggested that the Applicant teaches a species of the claimed genus, which is a fusion protein comprising UbL^{R23}-lacZ whose structure is known, however, the function as claimed, *i.e.*, to be used for assessing the proliferative potential of malignant cells, is not supported by the teachings of the instant specification as the specification does not provide definite results of degradation of UbL^{R23}-lacZ in normal and malignant cells. It is further suggested, that while fusion proteins such as Ub-P-βgal or any other consisting of SEQ ID NOs 2, 4-12 and operably linked to reporter genes are taught, they have not been transfected into malignant cells and their normal counterparts and therefore the function of these proteins as claimed is not described in the specification. The Examiner also suggests that as the number of UbL proteins is greater then disclosed in the application, the scope of the claims covers any UbL, and the genus of UbL encoding DNA that is claimed is not sufficiently described. Provision of nucleic acid molecules of SEQ ID NO:2-12 has not been found to be sufficient for identifying all species of UbL. Further, the Examiner suggests that the term "operably linked" as defined on

page 19 does not state how the UbL and reporter gene are connected. Moreover, claims 10-12 are rejected because step b) of claim 10 is lacking description of assessing the half-life of any fusion protein in a malignant cell and its normal counterpart transformed with DNA encoding said fusion protein.

Thus, the Examiner concludes that given the lack of structural and functional characteristics of representative species as encompassed by the claims and lack of real experiments providing evidence of relationship between the degradation of claimed fusion proteins in mammalian cells and their rate of growth, Applicant has failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicant was in possession of the claimed invention as filed. Applicant respectfully disagrees.

The present specification teaches that, when a reporter protein is fused to an ubiquitin-like domain, the stability of the reporter protein is decreased in actively growing cells as compared to the stability of the reporter protein in normal quiescent cells. Accordingly, in an effort to advance the prosecution of the instant application, Applicant has amended base claim 6 to clarify suitable UbL domains, namely amino acid sequences represented by SEQ ID NO:2-12, for use in the DNA construct of the present invention. Claim 8 has therefore been canceled. Further, claim 10 has been amended to read on a DNA construct encoding a fusion protein for assessing the proliferative potential of a target cell, wherein the DNA construct comprises a fusion between a UbL domain and a reporter molecule such that the reporter molecule of the fusion protein encoded by the DNA construct has a decrease in stability in an

actively growing cell when compared to the stability of the reporter molecule of the fusion protein encoded by said DNA construct in a normal quiescent cell. Support for these amendments can be found throughout the specification (*e.g.*, at pages 14-17 and in Figures 7 and 9).

MPEP 2163.02 indicates that "an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Given the guidance provided in the instant specification regarding the utility of a ubiquitin-like domain to destabilize reporter molecules in actively growing cells, one of skill in the art could readily prepare DNA constructs comprising a UbL domain, particularly of SEQ ID NO:2-12, and a reporter and carry out methods for using the same. The functional and structural characteristics of each essential element of the DNA construct and the relationship of these elements to stability in actively growing cells are specifically disclosed in the instant application to permit one skilled in the art to immediately envisage the claimed fusion protein of the invention. For example, Figures 7 and 9 teach increased destabilization of two reporter proteins in actively growing cells when the reporter protein is fused to a UbL domain, namely UbL^{R23}. Further, experimental data provided in the instant specification (pages 41 and 42) show binding of multiple human and yeast UbL domains, including UbL^{R23}, to proteasome proteins. Therefore, one of skill in the art would anticipate that ubiquitin-like domains from any

species which bind to proteasome proteins and share similar 3-dimensional structure as taught by van der Spek et al., 1996 (see page 39, lines 7-10) would function to destabilize a reporter protein in actively growing cells. The specification further discloses suitable target cells (*i.e.*, cells of divergent organisms from yeast to humans; page 16, lines 33-34) which can be analyzed to determine their proliferative potential and exemplifies the utility of the DNA construct and method of the present invention in a model cell (*i.e. Saccharomyces cerevisiae*) representative of these target cells.

Applicant respectfully disagrees with the Examiner's suggestion that the term "operably linked" lacks structural description in the Application. As acknowledged by the Examiner, page 19, teaches that operably linked describes the fusion of a nucleic acid sequence encoding an UbL domain to a second nucleic acid sequence encoding a protein of interest such that expression of the fused molecule results in the production of a fusion protein. Given this and the teachings provided in the examples which describe UbL domains with reporter molecules directly fused to the C-terminus (page 28, lines 5-35) and N-terminus (page 41, lines 5-7) of the UbL domain, one of skill could visualize constructs containing a UbL domain operably linked to a reporter molecule.

Therefore, the specification meets the written description requirement set forth under 35 U.S.C. §112, first paragraph, in providing the skilled artisan with fusion proteins for detecting the proliferative potential of a target cell. It is therefore respectfully requested that this rejection be withdrawn.

Claims 6-12 have also been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner suggests that the specification fails to teach mammalian, normal and malignant, cells transformed with such DNA constructs and any data related to degradation of expressed fusion peptides in said mammalian cells. It is suggested that the nature and breadth of the claimed invention encompasses any DNA construct encoding for UbL-reporter, or encoding for fusion wherein UbL is any one of SEQ ID NO:2-12 operably linked to any reporter, or any UbL operably linked to a reporter identified in claim 9, wherein said proteins are used in a method of assessing the proliferative potential of malignant cells. The Examiner acknowledges that the art of construction of DNA molecules encoding fusion proteins is high; however, because the structure of the claimed fusion polypeptide to be used and the method of use itself are lacking enabling description, one skilled in the art would be forced to perform undue experimentation with low probability of success. It is suggested that the mechanism of degradation of linear molecules consisting of UbL-any protein is not disclosed and because degradation of a particular UbL-reporter depends on the degradation pathway, the structure of the UbL and the linkage between UbL and the reporter (as evidenced by U.S. Patent 5,132,213), the specification must provide a reasonable amount of guidance with respect to the direction in which experimentation should proceed so that fusion proteins have the function used in the method for assessing the proliferative potential of malignant cells. Applicant respectfully disagrees.

MPEP 2164.01 states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well-known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. Denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrick GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The instant specification teaches and enables the use of UbL domains fused to reporter molecules for assessing the proliferative potential of target cells containing said fusion proteins. The examples disclose the nature of the fusions (*i.e.*, a direct fusion of a UbL to a reporter as discussed *supra*) and teach that proteins containing UbL domains such as UbL^{DSK}, UbL^{R23}, UbL^{HRB} fused to reporters such as GST and β-gal, bind to the proteasome (see pages 41 and 42), wherein the binding is more favorable in actively growing cells (*e.g.*, GST-UbL^{DSK}; see page 44, lines 20-22), leading to an decrease in the stability of the fusion protein in actively growing cells (*e.g.*, UbL^{R23}-βgal; see pages 32-33). Given these teachings in view of what is well-established in the art regarding UbL-reporter junction sequences for generating a stable UbL-reporter protein (see Table 1 of U.S. Patent 5,132,213), one of skill in the art could readily generate and predictably use such a fusion protein to assess the proliferative potential of a target cell. Exemplifying each and every UbL-reporter protein combination is not required of the

Applicant to satisfy the enablement requirement set forth under 35 U.S.C. §112, first paragraph. Therefore, withdrawal of this rejection is respectfully requested.

IV. Rejection Under 35 U.S.C. §102

Claims 6, 7 and 9 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 5,132,213. The Examiner suggests that this reference discloses constructs of Ub (ubiquitin is a ubiquitin-like protein) and βgal linked directly or through one or two amino acids and DNA and vectors encoding the same. The Examiner acknowledges that this reference does not teach the fusion protein for assessing the proliferative potential of malignant cells; however, because this limitation is in the preamble, it is not an internal feature of the fusion protein encoded by the claimed DNA construct and does not add the patentable weight to the claim.

As discussed *supra*, Applicant has amended base claim 6 to read on a DNA construct encoding a fusion protein wherein the UbL domain is selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12.

MPEP 2131 states "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

While U.S. Patent No. 5,132,213 teaches an UbL-reporter fusion protein comprising a single ubiquitin repeat having the N-

terminal amino acid sequence Met-Gln-Ile-Phe-Val fused to the lacZ gene, this reference does not teach a UbL domain of SEQ ID NO:2-12. Accordingly, because U.S. Patent 5,132,213 does not teach each and every element of the claimed invention as set forth by MPEP 2131, it does not anticipate it. It is therefore respectfully requested that this rejection be withdrawn.

V. Conclusion

The Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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